**Citation:**

Larsson SC, Friberg E, Wolk A. Carbohydrate intake, glycemic index and glycemic load in relation to risk of endometrial cancer: A prospective study of Swedish women. *Int J Cancer.* 2007 Mar 1;120(5):1103-7.

**PubMed ID:** 17131331

**Study Design:**

Prospective Cohort Study

**Class:**

B - Click here for explanation of classification scheme.

**Research Design and Implementation Rating:**

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

To examine prospectively the associations of glycemic index and glycemic load as well as carbohydrate intake with the risk of endometrial cancer in a large population-based cohort of Swedish women.

**Inclusion Criteria:**

- Women born between 1914 and 1948
- Resident of Uppsala and Vastmanland counties (Sweden)

**Exclusion Criteria:**

- Incorrect or missing national registration number
- Missing date on the questionnaire, date of moving out of the study area, date of death
- Implausible values for energy intake (3 standard deviations from the mean value for log-transformed energy intake) and women with a cancer diagnosis (other than nonmelanoma skin cancer) or who had undergone a hysterectomy before baseline

**Description of Study Protocol:**

**Recruitment**

All women born between 1914 and 1948 and resident of Uppsala and Vastmanland counties (Sweden) were mailed an invitation to participate between 1987 and 1990.

**Design:** Prospective Cohort Study, Swedish Mammography Cohort

**Blinding used (if applicable):** not applicable

**Intervention (if applicable):** not applicable

**Statistical Analysis**

- Cox proportional hazards models
- Controlled for age and calendar time, conducted stratified models by age at follow-up and years of enrollment.
- Forward selection was used to construct multivariate models including education, BMI, age at menarche, oral contraceptive use, age at first birth, parity, age at menopause, postmenopausal hormone use, and menopausal status.

**Data Collection Summary:**

**Timing of Measurements**

- Participants completed a diet questionnaire at enrollment and another questionnaire at follow-up in 1997.
- Follow-up time was counted from the date of enrollment to the date of diagnosis of endometrial cancer, date of death, date of hysterectomy, date of migration, or June 30, 2005.
- 15.6 y follow-up

**Dependent Variables**

- Endometrial cancer
- Incident cases of endometrial cancer were ascertained by record linkages with the national and regional Swedish Cancer registers.

**Independent Variables**

- Quintiles of carbohydrate, glycemic index and glycemic load
- Participants completed a diet questionnaire (64 food items) at enrollment and another questionnaire at follow-up (96 food items) in 1997.

**Control Variables**

- Age and calendar time
- Education
- BMI
- Age at menarche
- Oral contraceptive use
- Age at first birth
- Parity
- Age at menopause
- Postmenopausal hormone use
- Menopausal status

**Description of Actual Data Sample:**

**Initial N**: 61,226 women for the main analysis; 36,369 women for analyses using data from the second questionnaire

**Attrition (final N):** as above. Mean follow-up time was 15.6 years with a total of 952,629 person-years

**Age**: 39-73 years at baseline in 1987

**Ethnicity**: Swedish

**Other relevant demographics**:

**Anthropometrics** BMI was similar across quintiles of glycemic load

**Location**: Uppsala and Vastmanland counties, Sweden

**Summary of Results:**

**Rate Ratios (RRS) and 95% CIS of Endometrial Cancer According to Quartiles of Carbohydrate Intake, Glycemic Index, and Glycemic Load Among 61,226 Women in the Swedish Mammography Cohort (1987-2005)**

| | Quintile | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | $p_{trend}$ |
| Carbohydrate intake (g/day) | | | | | | |
| Range (median) | <211 (201) | 211-223 (218) | 223-233 (239) | 234-245 (240) | 246 (256) | |
| No. of cases | 96 | 124 | 112 | 142 | 134 | |
| Person-years | 191,736 | 193,109 | 190,759 | 189,306 | 187,719 | |
| Rate ratios (95% CI) | 1.00 | 1.19 (0.90-1.56) | 1.03 (0.78-1.36) | 1.24 (0.95-1.61) | 1.12 (0.85-1.47) | 0.42 |
| Glycemic index | | | | | | |
| Range (median) | <75.7 (73.9) | 75.8-78.3 (77.2) | 78.4-80.6 (79.6) | 80.7-83.3 (81.9) | 84.4 (85.5) | |
| No. of cases | 110 | 130 | 126 | 119 | 123 | |
| Person-years | 190,283 | 196,555 | 190,717 | 186,075 | 188,999 | |
| Rate ratios (95% CI) | 1.00 | 1.09 (0.84-1.41) | 1.06 (0.81-1.37) | 1.01 (0.78-1.32) | 1.00 (0.77-1.30) | 0.79 |
| Glycemic load | | | | | | |
| Range (median) | <164 (155) | 164-176 (170) | 177-186 (181) | 187-199 (193) | 200 (210) | |
| No. of cases | 100 | 123 | 115 | 126 | 144 | |
| Person-years | 191,609 | 193,398 | 190,433 | 190,368 | 186,821 | |
| Rate ratios (95% CI) | 1.00 | 1.14 (0.87-1.50) | 1.03 (0.78-1.36) | 1.09 (0.83-1.42) | 1.15 (0.88-1.51) | 0.41 |

Cox proportional hazards models were used to calculate rate ratios adjusted for age in months. Carbohydrate intake, glycemic index and glycemic load were adjusted for total energy intake using the residual method.[ 25]

**Rate Ratios and 95% CIS of Endometrial Cancer According to Quartiles of Carbohydrate Intake, Glycemic Index, and Glycemic Load, Stratified by Body Mass Index Among 61,226 Women in the Swedish Mammography Cohort (1987-2005)1**

| | Quintile | | | | | |
|---|---|---|---|---|---|---|
| **Body mass index** | **1** | **2** | **3** | **4** | **5** | ***p*trend** |
| <25 kg/m$^2$ (*n* = 243 cases) | | | | | | |
| Carbohydrate | 1.00 | 1.06 (0.70-1.61) | 0.89 (0.58-1.37) | 1.19 (0.79-1.79) | 1.01 (0.66-1.54) | 0.83 |
| Glycemic index | 1.00 | 1.16 (0.78-1.73) | 0.84 (0.55-1.27) | 0.89 (0.58-1.37) | 1.05 (0.69-1.59) | 0.61 |
| Glycemic load | 1.00 | 0.89 (0.59-1.36) | 1.13 (0.75-1.70) | 1.09 (0.72-1.64) | 0.94 (0.61-1.44) | 0.96 |
| 25-<30 kg/m$^2$ (*n* = 192 cases) | | | | | | |
| Carbohydrate | 1.00 | 1.32 (0.79-2.21) | 0.91 (0.53-1.57) | 1.20 (0.72-2.00) | 1.39 (0.84-2.33) | 0.27 |
| Glycemic index | 1.00 | 1.35 (0.83-2.19) | 1.24 (0.75-2.05) | 1.19 (0.73-1.96) | 0.86 (0.50-1.46) | 0.55 |
| Glycemic load | 1.00 | 1.27 (0.76-2.14) | 1.15 (0.69-1.93) | 1.07 (0.64-1.79) | 1.26 (0.76-2.10) | 0.59 |
| 30 kg/m$^2$ (*n* = 147 cases) | | | | | | |
| Carbohydrate | 1.00 | 1.38 (0.70-2.72) | 1.19 (0.62-2.28) | 0.99 (0.51-1.95) | 1.68 (0.86-3.29) | 0.35 |
| Glycemic index | 1.00 | 0.82 (0.43-1.56) | 1.32 (0.71-2.44) | 1.03 (0.55-1.93) | 0.93 (0.50-1.74) | 0.99 |
| Glycemic load | 1.00 | 1.15 (0.62-2.14) | 0.69 (0.34-1.40) | 1.05 (0.55-2.01) | 1.57 (0.82-2.99) | 0.18 |

1 Cox proportional hazards models were used to calculate rate ratios adjusted for age in months. Carbohydrate intake, glycemic index and glycemic load were adjusted for total energy intake using the residual method.[ 25] The number of cases does not add up to the total number of cases (*n* = 608) owing to missing data on body mass index.

**Key Findings**

No overall association between carbohydrate intake, glycemic index or glycemic load and incidence of endometrial cancer.

The rate ratios for the highest versus the lowest quintile were 1.12 (95% CI: 0.85 - 1.47) for carbohydrate intake, 1.00 (95% CI: 0.77 - 1.30) for glycemic index and 1.15 (95% CI: 0.88 - 1.51) for glycemic load.

However, among obese women (BMI > 30), endometrial cancer incidence was nonsignificantly elevated in the top versus bottom quintiles of carbohydrate intake (rate ratio = 1.68; 95% CI: 0.86 - 3.29) and glycemic load (rate ratio = 1.57, 95% CI: 0.82 - 2.99).

Tests for interaction between physical activity and carbohydrate intake or glycemic load in relation to endometrial cancer were not statistically significant (*p*-interaction = 0.37 for carbohydrate intake; *p*-interaction = 0.20 for glycemic load).

However, among women who were both physically inactive and overweight (BMI  25 kg/$m^2$), the age-adjusted RRs for the highest *versus* the lowest quartile were 1.90 (95% CI, 0.84-4.31) for carbohydrate intake and 2.99 (95% CI, 1.17-7.67) for glycemic load.

**Author Conclusion:**

In summary, in this prospective study, we observed no overall association of carbohydrate intake, glycemic index or glycemic load with endometrial cancer risk. However, our findings suggest that a high carbohydrate intake and a high-glycemic load diet may be associated with an increased risk of endometrial cancer among overweight women with low physical activity.

***Reviewer Comments:***

*Authors note the following limitations:*

- *Dietary intake assessed with self-administered food frequency questionnaire, which will inevitably lead to some error in the measurement of diet and the calculation of glycemic index and glycemic load*
- *Glycemic index values of some foods are currently based on results reported in only 1 or 2 studies, and those studies often had small sample sizes*
- *Information on physical activity was only available in the second (1997) questionnaire*
- *Observational study - cannot exclude the possibility that unmeasured confounding may have affected risk estimates*

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***Research Design and Implementation Criteria Checklist: Primary Research***

**Relevance Questions**

| | | |
|---|---|---|
| 1. | Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies) | Yes |

| | | |
|---|---|---|
| 2. | Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about? | Yes |
| 3. | Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice? | Yes |
| 4. | Is the intervention or procedure feasible? (NA for some epidemiological studies) | Yes |

**Validity Questions**

| | | |
|---|---|---|
| **1.** | **Was the research question clearly stated?** | Yes |
| 1.1. | Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified? | Yes |
| 1.2. | Was (were) the outcome(s) [dependent variable(s)] clearly indicated? | Yes |
| 1.3. | Were the target population and setting specified? | Yes |
| **2.** | **Was the selection of study subjects/patients free from bias?** | Yes |
| 2.1. | Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study? | Yes |
| 2.2. | Were criteria applied equally to all study groups? | Yes |
| 2.3. | Were health, demographics, and other characteristics of subjects described? | Yes |
| 2.4. | Were the subjects/patients a representative sample of the relevant population? | Yes |
| **3.** | **Were study groups comparable?** | Yes |
| 3.1. | Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) | N/A |
| 3.2. | Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? | N/A |
| 3.3. | Were concurrent controls used? (Concurrent preferred over historical controls.) | Yes |
| 3.4. | If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? | Yes |

| | | |
|---|---|---|
| 3.5. | If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) | N/A |
| 3.6. | If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")? | N/A |
| **4.** | **Was method of handling withdrawals described?** | Yes |
| 4.1. | Were follow-up methods described and the same for all groups? | Yes |
| 4.2. | Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.) | Yes |
| 4.3. | Were all enrolled subjects/patients (in the original sample) accounted for? | Yes |
| 4.4. | Were reasons for withdrawals similar across groups? | N/A |
| 4.5. | If diagnostic test, was decision to perform reference test not dependent on results of test under study? | N/A |
| **5.** | **Was blinding used to prevent introduction of bias?** | Yes |
| 5.1. | In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate? | N/A |
| 5.2. | Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) | N/A |
| 5.3. | In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded? | Yes |
| 5.4. | In case control study, was case definition explicit and case ascertainment not influenced by exposure status? | N/A |
| 5.5. | In diagnostic study, were test results blinded to patient history and other test results? | N/A |
| **6.** | **Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?** | Yes |
| 6.1. | In RCT or other intervention trial, were protocols described for all regimens studied? | N/A |
| 6.2. | In observational study, were interventions, study settings, and clinicians/provider described? | Yes |
| 6.3. | Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? | Yes |
| 6.4. | Was the amount of exposure and, if relevant, subject/patient compliance measured? | N/A |

| | | |
|---|---|---|
| 6.5. | Were co-interventions (e.g., ancillary treatments, other therapies) described? | N/A |
| 6.6. | Were extra or unplanned treatments described? | N/A |
| 6.7. | Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? | Yes |
| 6.8. | In diagnostic study, were details of test administration and replication sufficient? | N/A |
| **7.** | **Were outcomes clearly defined and the measurements valid and reliable?** | No |
| 7.1. | Were primary and secondary endpoints described and relevant to the question? | Yes |
| 7.2. | Were nutrition measures appropriate to question and outcomes of concern? | Yes |
| 7.3. | Was the period of follow-up long enough for important outcome(s) to occur? | Yes |
| 7.4. | Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? | Yes |
| 7.5. | Was the measurement of effect at an appropriate level of precision? | No |
| 7.6. | Were other factors accounted for (measured) that could affect outcomes? | Yes |
| 7.7. | Were the measurements conducted consistently across groups? | Yes |
| **8.** | **Was the statistical analysis appropriate for the study design and type of outcome indicators?** | Yes |
| 8.1. | Were statistical analyses adequately described and the results reported appropriately? | Yes |
| 8.2. | Were correct statistical tests used and assumptions of test not violated? | Yes |
| 8.3. | Were statistics reported with levels of significance and/or confidence intervals? | Yes |
| 8.4. | Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? | Yes |
| 8.5. | Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? | Yes |
| 8.6. | Was clinical significance as well as statistical significance reported? | Yes |
| 8.7. | If negative findings, was a power calculation reported to address type 2 error? | No |
| **9.** | **Are conclusions supported by results with biases and limitations taken into consideration?** | Yes |
| 9.1. | Is there a discussion of findings? | Yes |

| | | | |
|---|---|---|---|
| | 9.2. | Are biases and study limitations identified and discussed? | Yes |
| **10.** | **Is bias due to study's funding or sponsorship unlikely?** | | Yes |
| | 10.1. | Were sources of funding and investigators' affiliations described? | Yes |
| | 10.2. | Was the study free from apparent conflict of interest? | Yes |